

V 503/29287

M

L3 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
AN 2000:15500 CAPLUS
DN 132:220058
TI NELL-1 enhances mineralization in fetal calvarial
osteoblastic cells
AU Kim, David; Soo, Chia; Zhang, Xinli; Park, Howard; Wang, Yubert; Longaker,
Michael T.; Ting, Kang
CS Departments of Surgery and School of Dentistry, Section of Orthodontics,
Los Angeles, Medical Center, University of California, Los Angeles, CA,
USA
SO Surgical Forum (1999), 50, 599-601
CODEN: SUFOAX; ISSN: 0071-8041
PB American College of Surgeons
DT Journal
LA English
AB The association of NELL-1 expression with bone formation
and mineralization of the calvarial osteoblast-like cells was studied.
NELL-1 mRNA was faintly expressed from day 14 of
gestation with mild increase over the gestation period. Both primary rat
fetal calvarial cell cultures and MC3T3 cell cultures overexpressing
NELL-1 showed an increase in mineralization. Mouse cDNA
array results from NELL-1-infected MC3T3 cells showed
the expression modulation of the genes related to bone formation and
craniofacial development: downregulation in BMP-7 gene expression and
upregulation of Split Hand and Foot gene.

BEST AVAILABLE COPY

US03/29281

L3 ANSWER 7 OF 28 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
 AN 2001-300143 [31] WPIDS
 DNC C2001-092112
 TI Screening for an agent that alters bone mineralization, useful for
 facilitating bone calcification or repair, comprises contacting a cell
 containing NELL-1 gene with a test agent and detecting
 a change in NELL-1 gene expression level.
 DC B04 D16 D22
 IN TING, K
 PA (REGC) UNIV CALIFORNIA; (TING-I) TING K
 CYC 94
 PI WO 2001024821 A1 20010412 (200131)* EN 54
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
 NL OA PT SP SE SI SZ T2 UG ZW
 W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
 DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
 LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
 SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
 AU 2000079943 A 20010510 (200143)
 US 2003158602 A1 20030821 (200356)
 ADT WO 2001024821 A1 WO 2000-0527477 20001004; AU 2000079943 A AU 2000-79943
 20001004; US 2003158602 A1 US 1999-412297 19991005
 FDT AU 2000079943 A Based on WO 2001024821
 PRAI US 1999-412297 19991005
 AB WO 200124821 A UPAB: 20010607
 NOVELTY - Screening (M1) for an agent that alters bone mineralization
 comprises contacting a cell containing a NELL-1 gene
 with a test agent, and detecting a change in the expression level of the
 NELL-1 gene as compared to the expression in a cell that
 is not contacted with the test agent at a lower concentration.
 DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
 following:
 (1) pre-screening (M2) for a NELL-1 modulator
 comprises contacting a NELL-1 nucleic acid or protein
 with a test agent, and detecting specific binding of the test agent to the
 NELL-1 nucleic acid or protein;
 (2) increasing (M3) bone mineralization comprises increasing the
 concentration of a NELL-1 gene product in an
 osteogenic cell;
 (3) facilitating (M4) the repair of bone fractures comprises
 increasing concentration of a NELL-1 gene product at
 or near the fracture site;
 (4) facilitating (M5) the repair of a bone fracture comprises
 contacting the bone fracture site with a NELL-1
 protein;
 (5) bone graft material (I) comprising a biocompatible matrix and a
 NELL-1 protein capable of enhancing the formation of
 osseous tissue in the animal in which it is implanted; and
 (6) bone graft material, which is capable of inducing the formation
 of osseous tissue in the animal in which it is implanted, comprising a
 collagen conjugate containing 65-95 weight% reconstituted collagen and 5-35
 weight% NELL-1 protein.
 ACTIVITY - Osteopathic.
 Whole mouse embryo RNA analysis from fetal gestation day 7, 11, 14
 and 17 was performed. Adenovirus carrying NELL-1 cDNA
 was constructed and infected into rat fetal calvarial primary
 cell cultures and MC3T3 cell lines. Adenoviruses containing the beta
 -galactosidase gene were used as control and examined for efficacy of
 infection with different cell types. NELL-1 mRNA was
 faintly expressed from day 14 of gestation with mild increase over the
 gestation period. Both primary fetal calvarial and MC3T3 cell
 cultures over expressing NELL-1 showed an increase in
 mineralization over the beta -galactosidase control. Over expression of

WELL-1 enhanced mineralization in calvarial osteogenic primary cell cultures by approximately 30 folds on day 17-post infection compared to the control. Results confirmed that WELL-1 is closely associated with bone formation and it enhanced mineralization of the calvarial osteoblast-like cells.

MECHANISM OF ACTION - None given.

USE - (M1) and (M2) are useful for identifying agents that enhance bone mineralization (claimed).

(M3-5) are useful for repairing bone fractures, increasing bone density, or to induce bone repair (claimed).

(I) is useful as bone graft materials for the treatment of fractures (claimed) or to facilitate replacement or healing of prostheses or bone transplants.
Dwg.0/1

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKewed/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.